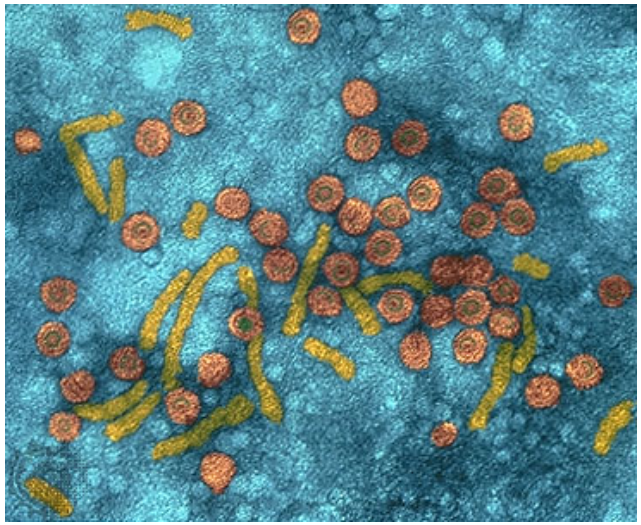

Dissolution as a Paradigm in Regulating Nanomaterials

Fred Klaessig

September 2017 ICEENN

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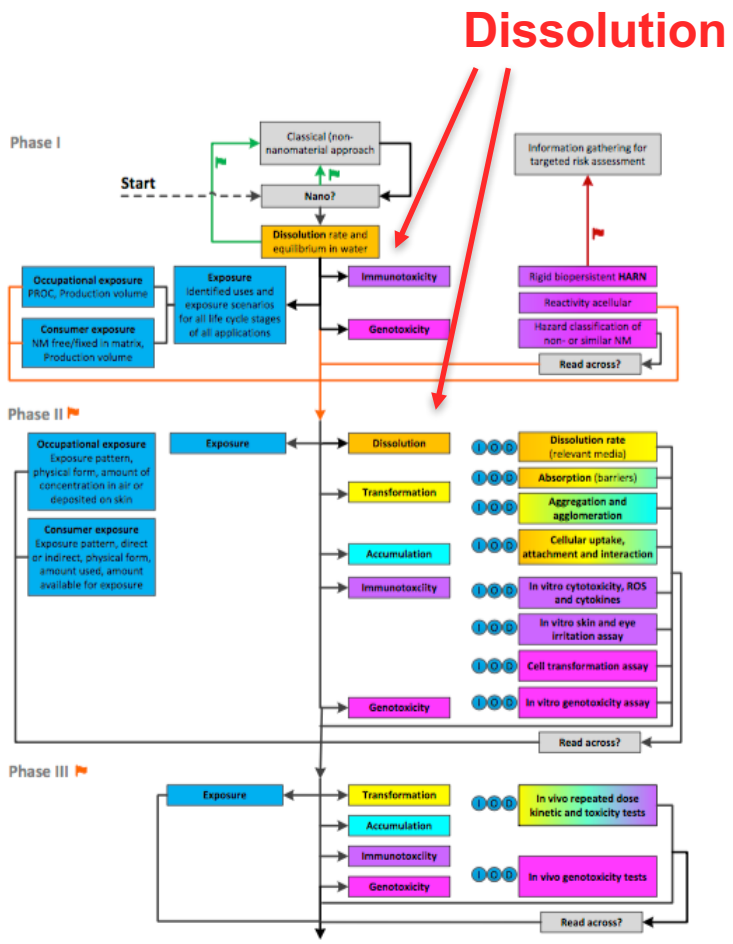
Background & Purpose

- 20 years specialty chemical R&D in water and process additives; and
- 11 years Evonik (Degussa) in technical and business (profit loss responsibility) roles
- Currently Active:
    - ISO/ TC 229 & ASTM E56
    - NCI's nanoWG (informatics)
    - UC-CEIN (outreach; stakeholders)
    - NanoFASE (advisory board)

Themes:

- Dissolution as a decision criterion
- Analogies to ζ-potential & VSSA
- Relation to nanoform & nanoscale form
- Dissolution kinetics and artifacts
- ASTM particle ontology & Nanoinformatics Roadmap implications



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VSSA: Over-simplified BET

- BET test is ‘easy’ & can calculate diameter
- SCCS colleagues proposed VSSA >60 m^2/cm^3, which became part of EC definition
- Examined in 9.3 million € NanoDefine:
  - Now 3 tests (BET & TEM & He pycnometry)
  - Threshold depends on shape (60,40, 20, +)
  - 7 of 21 samples ‘borderline; cautions on porous materials & does not explain NM-401
- SCCS views VSSA as a specification

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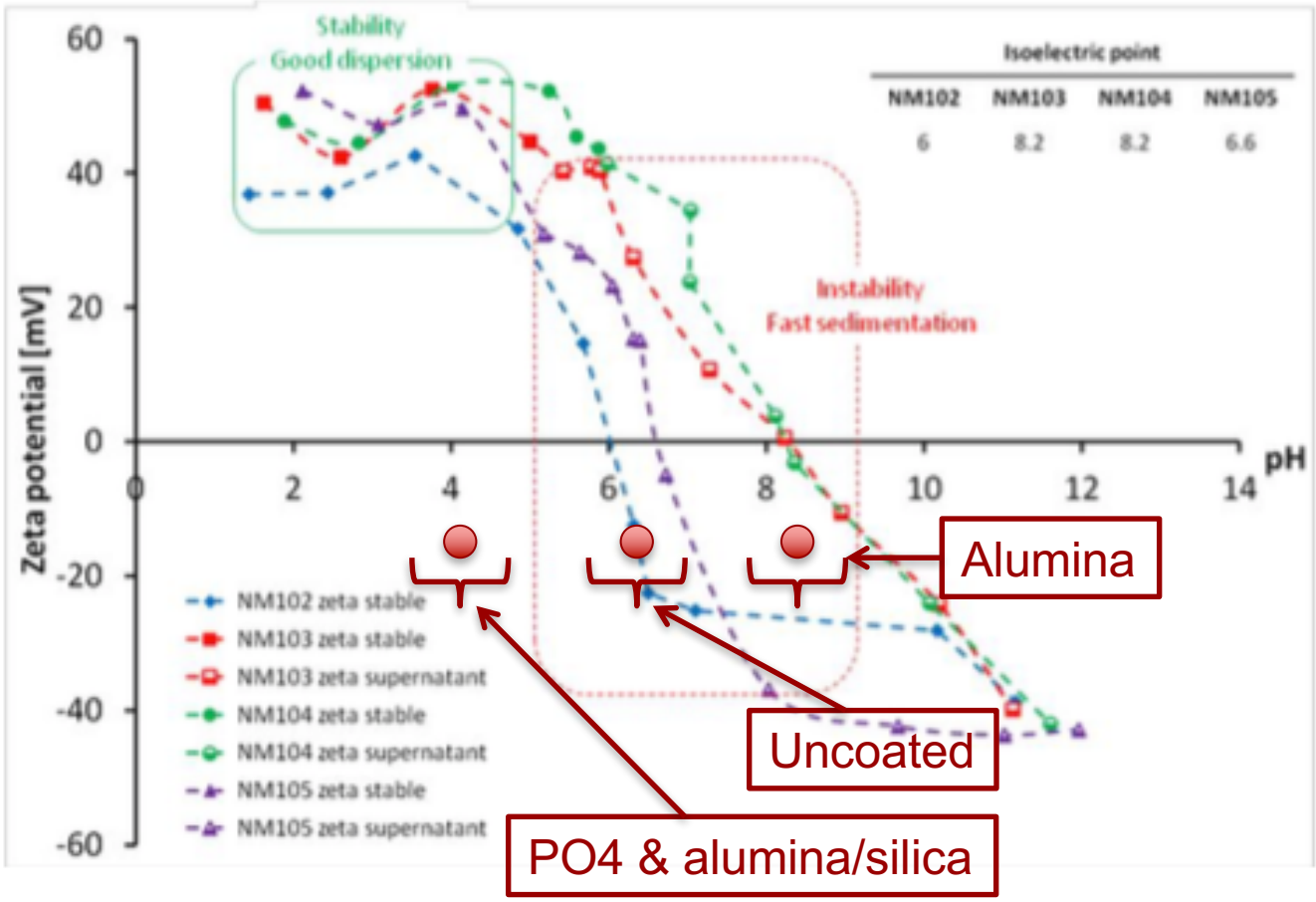
TiO2-i.e.p. fromNanogenotox



- Accounts for series by Morris (coated) & Warheit (uncoated)
- PO4 a process additive for morphology & perhaps dispersibility

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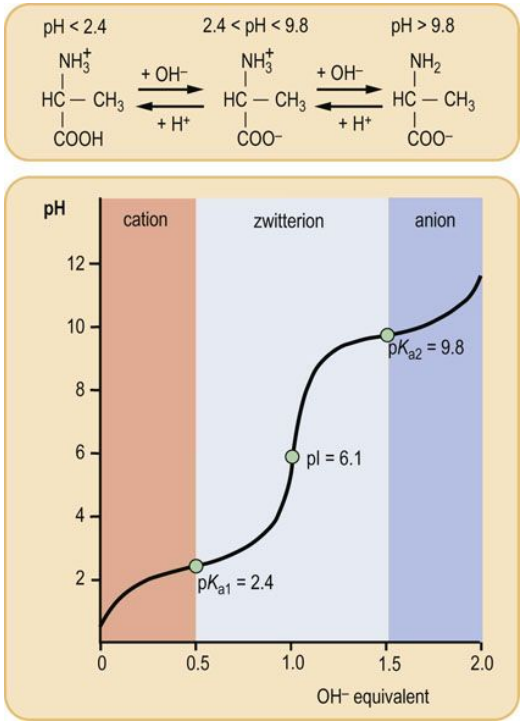
Zeta Potential and pI



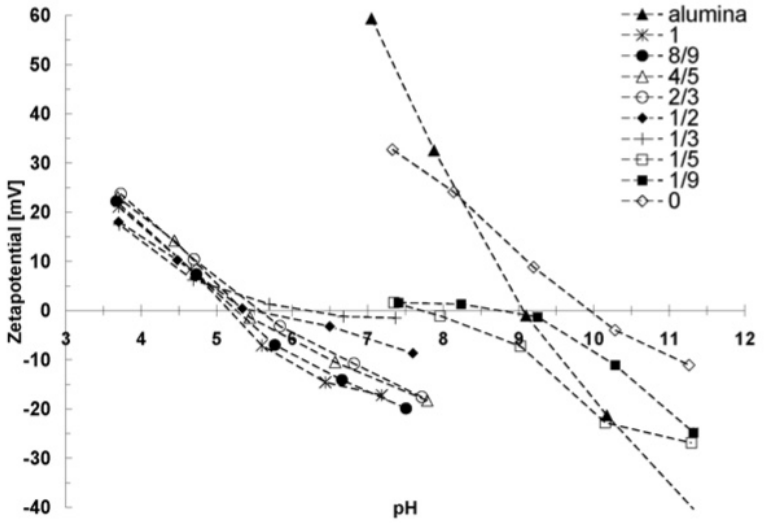


Figure 7.1 *Zetapotential measurements of 2 vol % alumina suspensions with and without adsorbed protein mixtures of different BSA to LSZ mol fractions after 16h. The total added protein amount was 0.5321 g which equals 1000 ng/cm^2 normalized to the alumina surface area.*

- Amino acids have an isoelectric point, pI, basis of electorphoresis
- For amino acid- 'coated' particles, the i.e.p.= the pI
- Amino acid mixtures lead to a blended ζ-potential & i.e.p.

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Dissolution Cautions

- Dissolution is a surrogate for biopersistence
- Dissolution in open systems, e.g. organism; but is solubility in static systems, e.g. buffers
  - Physical transport changes conditions
  - Kinetic mechanisms only partially explored
  - Adsorbed species may poison (inhibit) active sites (kinks, screw dislocations)
  - Similar challenges as in drug bioavailability testing
- When used as a decision criterion ‘forces’ an unwarranted threshold value

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ECETOC Threshold

- Proposing 100 mg/l as 'highly soluble'
  - Synthetic amorphous silica would be highly soluble and tox testing limited even though
  - fumed silica more inflammatory than quartz (accepted source of silicosis) or precipitated silica
- Uncertain origin of 100 mg/l target
  - Expert judgement in ISO and BAuA documents
  - Break point in selecting between OECD protocols
  - Likely from medical testing for bioavailability
- ECETOC experts did not base their proposal on data that included mode of action, etc.

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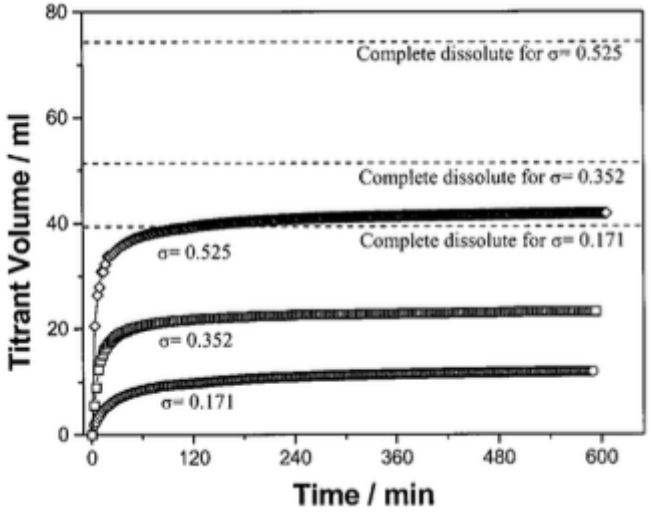
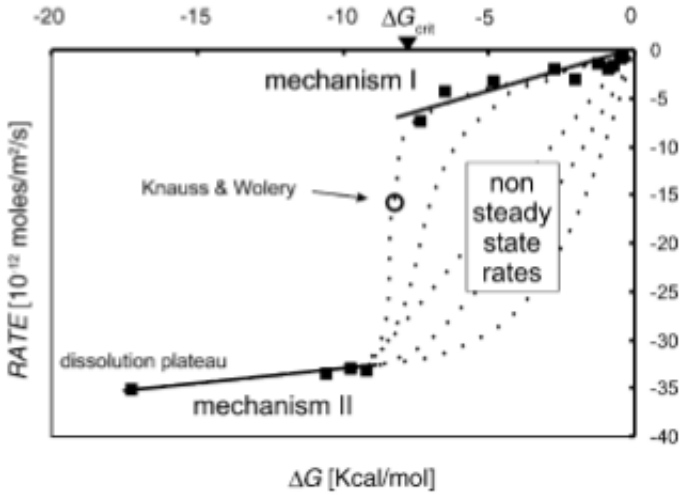
Dissolution Mechanisms



- Pit walls must be distant or pit may stall
- Critical pit size function of surface energy
- Limited to no dissolution if critical pit size ~particle diameter

- Flat-bottom pits become step waves
- Mech. II generates pits & step waves
- Mech. I is existing step waves only
- Critical ΔG switches mechanisms



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HAP (nano) as a Journey

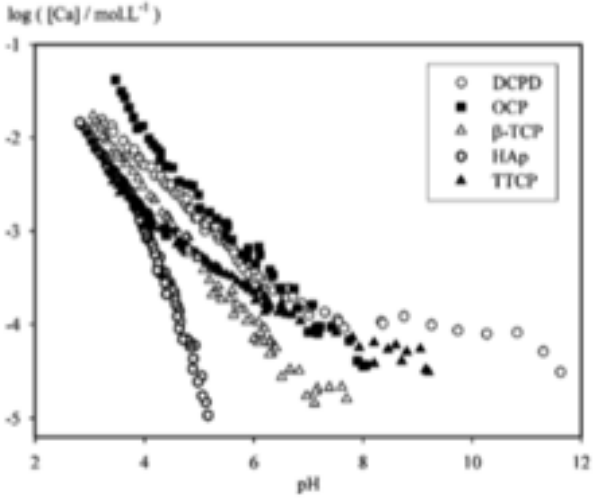

Figure 5. Solid titration solubility isotherms for HAp and (metastable) DCPD compared with solid titration curves for OCP, β-TCP, and TTCP (which produce HAp at the end-point).

Medium	pH	Value
DI	??	SCCS report <0.01 mg/l
Gastric	~2	FK expects near to complete dissolution
Gastric	~2	Westerhoff reports 30-40% persists
Intestine	~7.5	Powell reports HAP precipitation

Engineered n-HAP can pass through the stomach and act as a seed for physiological n-HAP

- Pepsin, saccharin, TKPP, sorbitol, polysorbate, t-butyl cresol may influence dissolution

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Sparingly Soluble Dissolution

- Powder upon entry into aqueous medium
  - Hydration/hydrolytic surface reactions
  - Adsorption of solutes
- Initial dissolution due to:
  - Surface roughening
  - Pit formation influenced by dislocations
- Asymptotic steady-state reflects
  - Step waves emanating from pits or edges
- Nanoscale particles in this category likely to persist for extended periods

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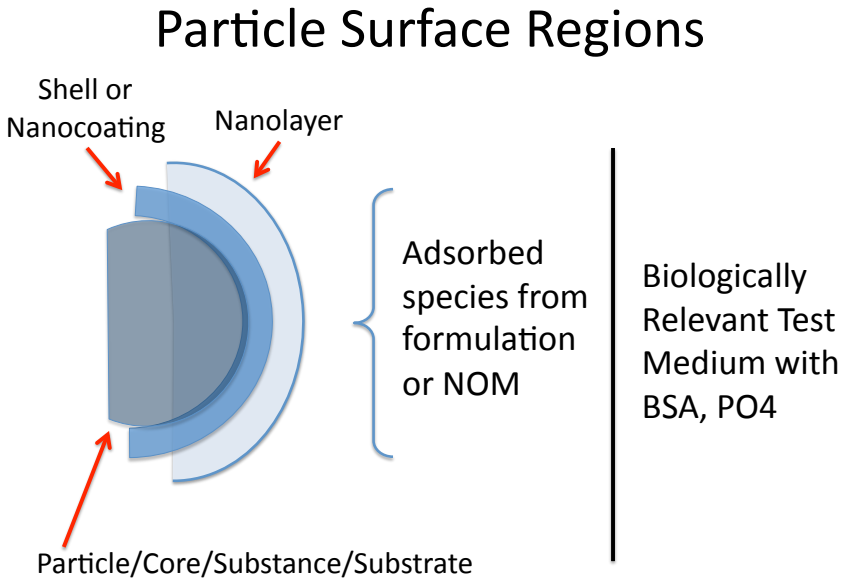
Particle 'Data Model'

- Useful in illustrating 'nanoform' distinctions
- Well suited to particle design (safer-by-design)
- nanoEHS properties can be assigned to a localized chemical composition
- Useful to modelers when selecting descriptors that align with particle life cycle



Commercial TiO2 Particles

89-93% of
(0.996 Ti/0.04 Al) O_2
solid solution to
favor rutile phase

6%
Alumina
Coating

1% glycerol (M212)
2% dimethicone (M262)

Al for refractive index
Coating suppresses photo- & chemical reactivity
Layer for powder wet-in

100% TiO2
80/20 anatase/rutile

No Coating

No Layer
(hydroxyl groups)

AEROXIDE® P25
Purity important to catalysis

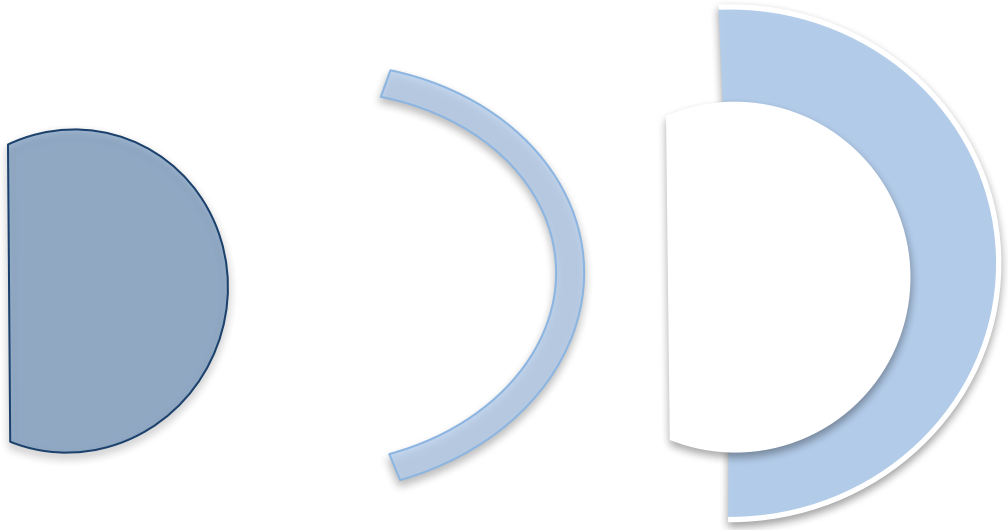
Properties & Localized Compositions

Shape
Band Gap
Dissolution

Dissolution

Surface Area
Zeta Potential
Dispersion stability

Localized Properties



Size = core + coating + layer
Light scattering
Viscosity

Compound properties

NPO Ontology

Grouping for zeta potential is by surface, not core chemistry

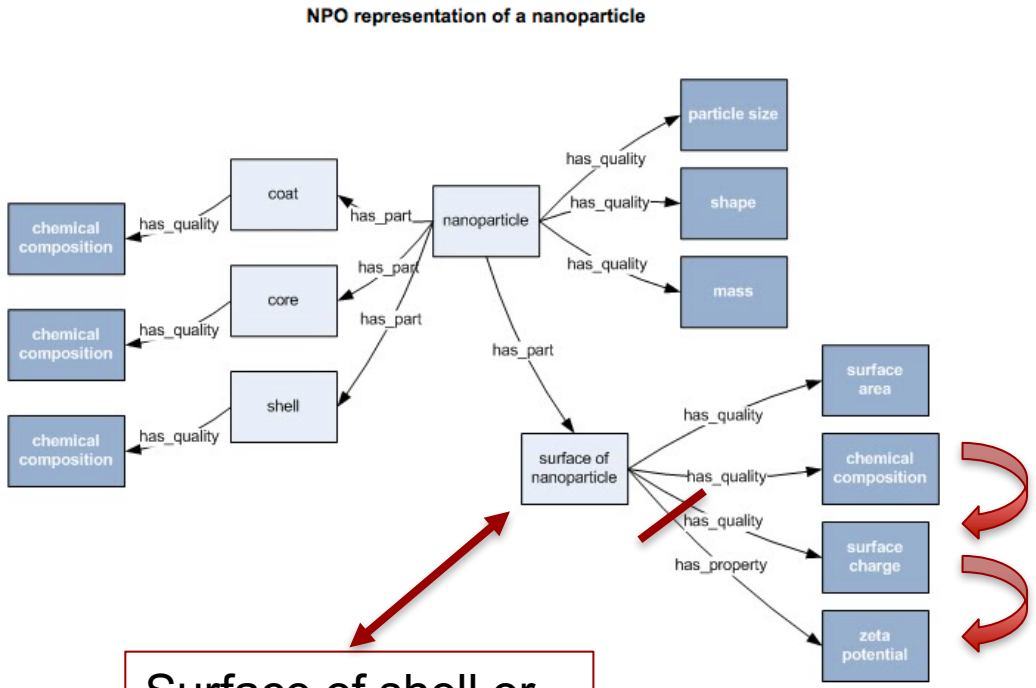
Nanoparticle Ontology was NIH- funded as part of NCI

Used in conjunction with ISA-TAB-nano in the caNanoLab database

eNanoMapper is the NANoREG counterpart

Zeta potential defined as the 'potential difference,' when it should be the charge arising from:

Ionic and dissociable chemical species on the surface or from adsorbed species on the surface



Surface of shell or coating, not of core

and must communicate that to the curator

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Layer Implications to nanoEHS

Coated particle considered a mixture, but

- Protein coronas influence toxicity
- F108 dispersed CNTs < CNT
- Alumina-coated CNTs < CNT
- Alumina-coated TiO_2 < TiO_2
- Pyrogenic SiO_2 > quartz > precipitated SiO_2

TiO_2 & SiO_2 implications will materialize during REACh dossier reviews

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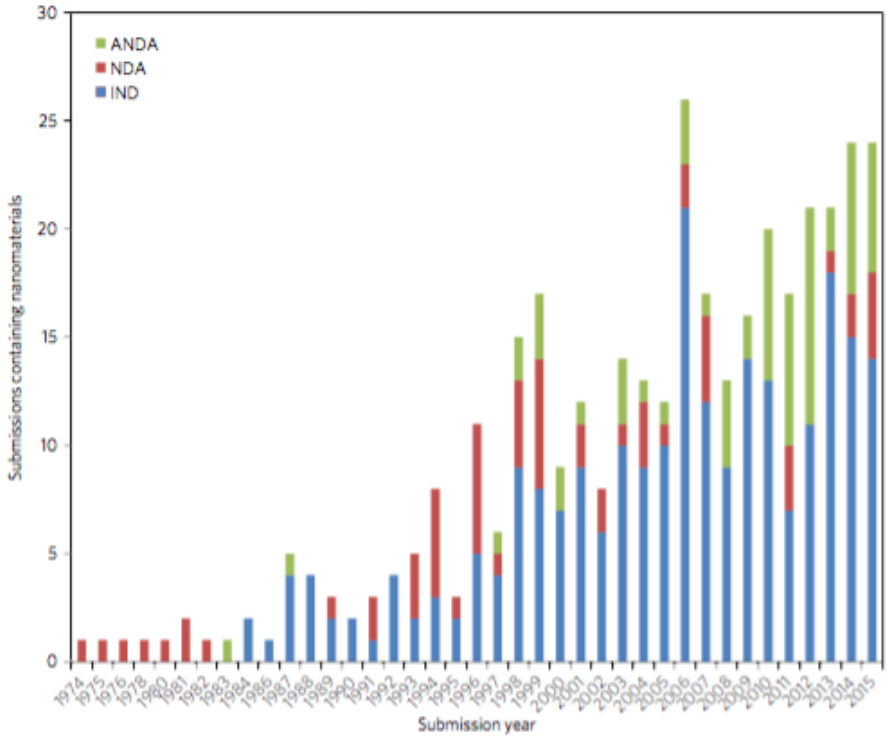
Nanomedicine Implications

Reformulations for Bioavailability & Biodistribution → Complex Microstructures Multifunctional & Multicomponent

- Total is 359
  - 234 INDs
  - 62 NDAs
  - 63 ANDAs
- Of the 234 INDs
  - 44 became NDAs
  - 34 were approved
- 1st Generation
  - Liposomes (33%)
  - Nanocrystals (23%)
  - Fe-Polymer emulsions & micelles (14%)



D'Mello *et al.*, NNANO.2017.67

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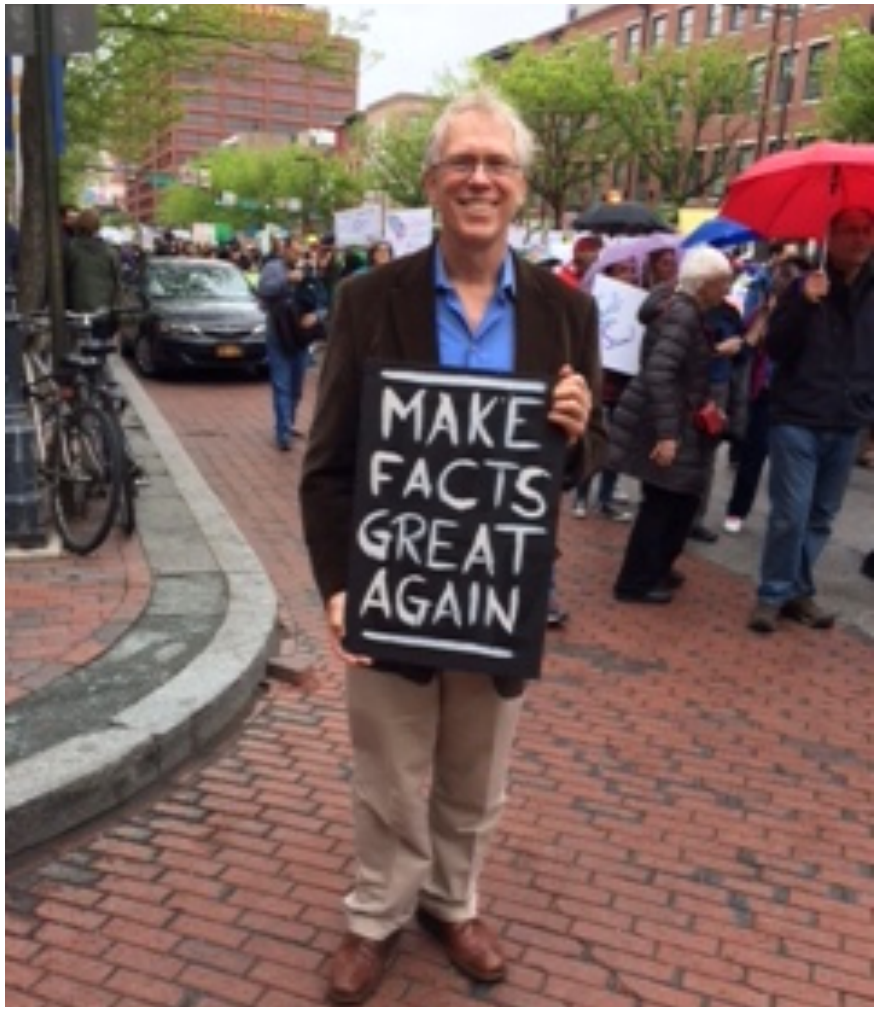
Summary

Premature to use dissolution as a decision criterion

Dissolution data should supplement toxicity studies and used to select controls

The particle ‘data model,’ in the Nanoinformatics 2030 Roadmap, is one method of compiling dissolution results

Opportunities to coordinate work with nanomedicine



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Thank You

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ICEENN Update

- 3 Sept. training workshop (REACh & TSCA); & 4-6 conference
- Same organizing committee as EU-US meeting & there is some overlap in topics:
  - Environmental release & modelling (Praetorius & Domerc)
  - Regulation, standardization, stakeholder involvement
  - Post-Brexit implications
- John Rumble (FutureNanoNeeds) panel discussions on categorization:
  a. Importance of categorization
  b. New Approaches
  c. Overcoming barriers

EU-US Update

Meeting 7 & 8 Sept. with themes being:

1. Bridging the nanoEHS-regulatory gap
   a. "Warranting" data for regulators
   b. Vicki Bier game theory, not decision theory, & applying to grouping
   c. Responses from Legal, Insurance, Industry
2. Nanoinformtics (Hendren)
3. Nanomanufacturing & -fabrication (Tinkle)
4. Nanomedicine- standardization (Patri)
5. Community of Research discussions

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NanoComput Report I

- Reads like one of my e-mails: comprehensive and very, very long…454 pages
- ISA-TAB-nano mentioned 15 times
- Overall, good overlap, no conflict with 2030 Roadmap and nanoWG discussions
- The length works against clarity; the Road-map's brevity leaves goals unsubstantiated
- JRC, unlike NIST, has an advisory role, which leads to more generalized recommendations

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NanoComput Report II

Agreements are manifold

- QSPRs & QSARs experience is undissociated molecules; Modes of toxicity unknown
- 44 QSPRs (solubility most frequent)
- 78 QSARs (cytotoxicity most frequent)
- Some QSPRs useful to data gaps; only a few QSARs
- Fate (dispersal) modeling has 2 categories:
  - Material Flow → LearNano & MendNano
  - Process-based → functional assays
- Science is fragmented & data access limited
- Fabulous case history analyses in appendices

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NanoComput III

Major differences are administrative

- Single hub vs. federated databases
- Implement quality guidelines (top down)
- Models should have “concrete regulatory applications in mind”
- Public dissemination should be a “contractual obligation”

- Not addressed regulatory uncertainty and statutory evidence rules

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